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A promising new strategy for monitoring EPP therapy

Erythropoietic protoporphyria (EPP) is a rare inherited disorder characterised by acute photosensitivity that often presents in early childhood. EPP has been reported worldwide, with the estimated Scottish and UK prevalences being 1:43,500¹ and 1:143,000² respectively. EPP was first described in 1961,³ and is caused by mutations in ferrochelatase (FECH), the enzyme that catalyses iron insertion into protoporphyrin IX (PPIX) to form haem. Reduced ferrochelatase activity results in PPIX accumulation in the skin, blood cells and skin blood vessels that causes stinging, tingling, burning or prickling upon sun exposure and which can persist for many days. This painful phototoxic reaction is rarely responsive to analgesia meaning that EPP patients are often fearful of the sun with a significant impact on quality of life. Many patients also experience a 'priming phenomenon' in which sunlight exposure primes the skin so that shorter periods of subsequent sun exposure cause symptoms.⁴

Whilst a number of therapies have been trialled for EPP, difficulties in objective assessment of disease activity and dependence on patient self-assessment, which is highly susceptible to the placebo effect, has meant that treatment efficacy is often unclear.^{5,6} Being able to monitor the effectiveness of EPP treatments would provide much-needed clarity on their benefits and would represent a huge advance in the field.

In this issue of the BJD, Heerfordt and Wulf describe a method for dynamically measuring PPIX levels in the skin of EPP patients which could be used to monitor treatment efficacy by comparing the light dose required to elicit symptoms before and after treatment. In contrast to previous measurements of skin PPIX which relied on biopsies or inducing blister formation,⁷ the authors used a fluorescence photometer which has previously been used to measure methyl-aminolaevulinate (MAL) induced PPIX accumulation in photodynamic therapy⁸ to measure skin PPIX levels before and after PPIX photobleaching. By analysing skin PPIX alongside erythrocyte PPIX, the authors could correlate the level of skin PPIX with erythrocyte PPIX concentration as well as the pain and erythema induced by light. Their results confirm for the first time that high skin (or erythrocyte) PPIX levels are associated with an increased likelihood of photosensitivity in EPP patients.

By monitoring the dynamics of skin PPIX levels following illumination, their analysis also provides interesting insights into photopriming. EPP patients with high initial skin PPIX were more likely to have increased PPIX in their skin the day after illumination, although the speed of accumulation differed between patients. This may be attributable to differences in the rates of initial light induced PPIX leakage from erythrocytes and subsequent release from damaged blood vessels and endothelial cells, although it would be interesting to explore this further since modulating the release of PPIX could represent a viable therapeutic strategy.

Taken together, this important research helps explain why the sunlight tolerance of EPP patients varies both between patients and within the same patient from day-to-day,⁴ and applying this much-needed new method to interrogate the effectiveness of EPP treatments will be valuable.

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